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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,463	03/21/2005	Chantal Guillemette	6013-118US	7564

20988 7590 09/12/2007

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
09/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,463	GUILLEMETTE, CHANTAL	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-11,13-15 and 18-31* is/are pending in the application.

4a) Of the above claim(s) *18-29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 8-11, 13-15, 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 6, 2007 has been entered.

Claims 1-2, 8-11, 13-15, and 18-31 and are currently pending. Claims 1, 15, 23, and 31 have been amended. Claims 18-29 and 31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Therefore Claims 1-2, 8-11, 13-15, and 30 will be addressed herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified:

Claims 1-2, 8-11, 13-15, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn broadly to encompass a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, side effect or a variation in response to therapy to a biologically active compound that is metabolized through UGT1A9 glucuronidation, said method comprising: obtaining a nucleic acid sample from said individual, determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of the UGT1A9 gene of said individual, said variation comprising a T-275A substitution, whereby the presence of the polymorphic or haplotypic variation in said nucleotide sequence is indicative of said predisposition or susceptibility. Thus the claims are drawn to detecting the T-275A substitution of the UGT1A9 gene or any haplotype comprising the T-275A substitution of the UGT1A9 gene. The claims do not define any haplotype comprising the T-275A substitution of the UGT1A9 in terms of particular structure or function.

The specification at page 24 teaches ten novel polymorphic variations within the UGT1A9 promoter region. The specification also teaches several haplotypes of the UGT1A9 promoter region which are presented in Table 11. It is noted that the specification teaches mutations present only in the promoter of the UGT1A9 gene. However the claims are drawn to detecting any haplotype comprising the T-275A substitution of the UGT1A9 gene. While methods which specifically detect the T-275A substitution of the UGT1A9 gene meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus

required by the claims of any haplotype comprising the T-275A substitution of the UGT1A9 gene.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that 'An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case the specification does not teach a representative number of haplotypes comprising the T-275A substitution of the UGT1A9 gene. The specification in Table 11 teaches 21 haplotypes of the UGT1A9 gene, six of

which include the T-275A substitution. However, this disclosure is not considered to be representative of the broadly claimed genus of any haplotype comprising the T-275A substitution. The disclosed polymorphisms are limited to only the promoter region of the UGT1A9 gene. No polymorphisms have been disclosed in other portions of the gene. However the genus of polymorphisms in the UGTA19 gene is potentially large and it is possible that there are other polymorphisms in linkage disequilibrium with the T-275A substitution. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided. Yet, the claims as written are inclusive of a potentially large genus of haplotypes comprising the T-275A substitution of the UGT1A9 gene. While one could contemplate possible combinations of one or more polymorphic sites and the resulting haplotypes comprising nucleotide substitutions, deletions or additions at each and every position in the UGT1A9 gene and in other undefined genes that may be in linkage disequilibrium, such nucleotide variations are not considered to be equivalent to specific nucleotide variations associated with causing a an adverse reaction, side effect, or variation in response to a biologically active compound that is metabolized through UGT1A9 glucuronidation. Rather, polymorphisms and haplotypes in the UGT1A9 gene which collectively make up haplotypes that are associated with causing a an adverse reaction, side effect, or variation in response to a biologically active compound that is metabolized through UGT1A9 glucuronidation represent a distinct group of haplotypes which comprises

polymorphisms that are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type UGT1A9 gene and other unspecified genes does not allow the skilled artisan to envision all of the contemplated haplotypes encompassed by the claimed genus. Conception of the claimed invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following rejection has been modified:

3. Claims 1-2, 8-11, 13-15, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, side effect or a variation in response to therapy to a biologically active compound that is metabolized through UGT1A9 glucuronidation, said method comprising: obtaining a

nucleic acid sample from said individual, determining the presence of a T-275A substitution in the nucleotide sequence of the UGT1A9 gene of said individual, whereby the presence of the T-275A substitution in said nucleotide sequence is indicative of said predisposition or susceptibility, does not reasonably provide enablement for a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, side effect, or a variation in response to therapy with a biologically active compound that is metabolized through UGT1A9 glucuronidation said method comprising: obtaining a nucleic acid sample from said individual; and determining the presence of a haplotypic variation in the nucleotide sequence of the UGT1A9 gene of said individual, said variation comprising a T-275A substitution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, side effect or a variation in

response to therapy with a biologically active compound that is metabolized through UGT1A9 glucuronidation by detecting the presence of the T-275A substitution of the UGT1A9 gene or by detecting any haplotype comprising the T-275A substitution. Thus the claims read on any haplotypic variation comprising the T-275A substitution of the UGT1A9 gene.

Nature of the Invention

The claims are drawn broadly to a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, side effect or a variation in response to therapy with a biologically active compound that is metabolized through UGT1A9 glucuronidation. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches on page 1 that the UDP-glucuronosyltransferase enzymes are a set of enzymes that increase the polarity of xenobiotics, drugs, and endogenous compounds to facilitate their excretion from the body. Any perturbation in the glucuronidation pathway has the potential to modify the elimination, the detoxification or the pharmacokinetic parameters of a given drug, and consequently drug clearance. Thus human genetic variation leading to differences in the glucuronidation rates could influence the activity of drugs and other chemicals. The specification on page 16 further teaches that DNA samples from 201 Caucasian subjects were used to genotype the UGT1A9 gene. The specification further teaches on

page 24 ten polymorphic mutations within the UGT1A9 promoter region. The specification also teaches UGT1A9 promoter haplotypes (See Table 11). It is noted that Table 11 teaches the frequencies of these haplotypes in the populations, however the specification does not provide any information on the percentage of linkage disequilibrium between these SNPs. The specification does not teach any additional mutations in the UGT1A9 gene or any other genes which might be in linkage disequilibrium with the T-275A substation. In addition to genotyping, the effect of UGT1A9 polymorphic variations on live microsomes glucuronidation was determined. The specification states on page 25 that there was a positive correlation between the presence of the T–275A mutated alleles and higher glucuronidation rate with SN-38 (See Fig 12). Additionally the specification teaches that SN-38 is the pharmacologically active metabolite of the anticancer drug irinotecan which undergoes extensive glucuronidation in humans to form SN-38-G.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying additional haplotypes of the UGT1A9 gene comprising the T-275A substitution which are also associated with higher glucuronidation rate is highly unpredictable. Knowledge of the sequence of the wild type UGT1A9 gene does not allow one to immediately envision any of the polymorphic sites of the UGT1A9 gene that are in linkage disequilibrium with the T-275A substitution. The UGT1A9 gene is expected to contain numerous polymorphisms and therefore must also contain numerous haplotypes. This is supported by the teachings in the post filing date art of Carlini et al (Clinical Cancer Research 2005) teaches several additional polymorphisms

identified in the coding region, the promoter region, and non-coding regions of UGT1A9 (see page 1228). However, the specification does not teach a predictable means for identifying additional haplotypes comprising the T-275A substitution that are also associated with a higher glucuronidation rates. Further the knowledge in the art of additional genes on chromosome 2 does not allow one to readily envision polymorphisms in other genes with may be linked to the T-275A substitution of the UGT1A9 gene and which could thereby be used to determine whether an individual has a predisposition or susceptibility to an adverse reaction, side effect or variation in response to therapy with a biologically active compound that is metabolized through UGT1A9 glucuronidation.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches that the –275 mutation of the UGT1A9 gene is associated with higher glucuronidation rates with SN-38. To identify additional haplotypes comprising the T-275A substitution which are associated with higher glucuronidation rates with SN-38 and other biologically active compounds would require extensive experimentation. For example, such experimentation may involve sequencing the UGT1A9 gene of individuals and then exposing them to SN-38 or other biologically active compounds and then determining the glucuronidation rates. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional haplotypes comprising the T-275A substitution of the UGT1A9 gene which are associated with higher glucuronidation rates.

Working Examples:

Again the specification teaches the –275 mutation of the UGT1A9 gene is associated with higher glucuronidation rates with SN-38. There are no specific examples provided in the specification in which other haplotypes comprising the –275 mutated alleles were also associated with a higher glucuronidation rates.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims are not enabled because the specification does not teach a representative number of haplotypes comprising the T-275A substitution of the UGT1A9 gene. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the

unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Arguments

4. In the response filed July 6, 2007, the Applicant state that the written description rejection no longer applies in view of the amendments to recite "said variation comprising a T-275A substitution. This argument and the amendments to the claims have been fully considered but are not persuasive to overcome the present grounds of rejection. While the claims have been amended to recite a specific nucleotide variation, the claims now encompass detecting the presence of any haplotype comprising the T-275A substitution. However the Applicants have not provided sufficient evidence to establish that they were in possession at the time of filing of a representative number of haplotypes comprising the T-275A substitution. Thereby the written description requirement has not been satisfied for the claims as they are broadly written.

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. The most recent case law directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y.,2003. March 5, 2003.) noted "In effect, then, the '850 patent claims a method that cannot be practiced until one discovers a compound that was not in the possession of, or known to, the inventors themselves. Putting the

claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current situation since the breadth of the current claims comprises the use of haplotypes which the present inventors were not in the possession of, or which were not known to the inventors. In a genus that is possibly quite immense, the specification discloses only a limited number of haplotypes comprising the T-275A substitution. Further, as noted in Fiers v. Su.qano (25 USPQ2d, 1601), the Fed. Cir. concluded that "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility." Thereby, it is maintained that the disclosure of 6 specific haplotypes comprising the T-275A substitution is not representative of the broadly claimed genus.

Regarding the enablement rejection the Applicants have amended claims so that they now read on a nucleic acid sample (not any type of sample), a biologically active compound that is metabolized through UGT1A9 (not any biologically active compound), and a T-275A substitution (not any polymorphic or haplotypic variation in exon 1 or the promoter of UGT1A9 gene). The amendments have been fully considered any many of these amendments were sufficient to overcome various points made in the enablement rejection. However, the claims still lack enablement because the claim language encompasses any haplotype comprising a T-275A substitution of the UGT1A9 gene. The claims lack enablement because the specification does not teach how one could

identify additional haplotypes comprising the T-275A substitution that could also be used in the methods of the present invention. For these reasons the enablement rejection is maintained.

Additionally it is noted that the Applicants have provided two post filing date references. If the Applicants wish to have these references made of record they must be cited on an Information Disclosure Statement.

Response to Amendment

5. The declaration under 37 CFR 1.132 filed March 30, 2007 is sufficient to partially overcome the enablement rejection. Both the Declaration and the Applicants arguments have been fully considered. The Applicants have submitted a declaration by Chantal Guillemette providing evidence that demonstrates that the determination of whether a drug is metabolized through UGT1A9 glucuronidation can be assessed routinely by using the test available from BD Bioscience. The Examiner recognizes this was well known in the art at the time of the invention and has therefore changed the scope of the previously presented enablement rejection. Thus the claims are enabled for "a biologically active compound that is metabolized through UGT1A9 glucuronidation".

Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

BJ FORMAN, PH.D.
PRIMARY EXAMINER